REPORTS

Characteristics Relating to Ovarian Cancer Risk: Collaborative Analysis of Seven U.S. Case-Control Studies. Epithelial Ovarian Cancer in Black Women

*Esther M. John, Alice S. Whittemore, Robin Harris, Jacqueline Itnyre, Collaborative Ovarian Cancer Group**

Background: **Previous epidemiologic studies of ovarian cancer have focused chiefly on White women, who have a higher incidence of ovarian cancer than Black women. No study has previously examined risk factors for ovarian cancer among Black women.** *Purpose:* **This study was designed to evaluate the risk of epithelial ovarian cancer in Black women in relation to reproductive characteristics such as pregnancy, oral contraceptive use, and breast-feeding, and to determine whether differences in reproductive factors between Black and White women account for differences in ovarian cancer incidence.** *Methods:* **Combining interview data from seven case-control studies, we compared reproductive characteristics of 110 Black case subjects with a diagnosis of epithelial ovarian cancer between 1971 and 1986 with characteristics of 251 Black population control subjects and 114 Black hospital control subjects. We also compared the prevalence of reproductive factors in 246 Black population control subjects and 4378 White population control subjects and estimated the fraction of Black-White differences in ovarian cancer incidence attributable to racial differences in prevalence of these characteristics.** *Results:* **Decreased risks of epithelial ovarian cancer in Black women were associated with parity of four or higher (odds ratio [OR] = 0.53; 95% confidence interval [CI] = 0.25-1.1), breast-feeding for 6 months or longer (OR = 0.85; 95% CI = 0.36-2.0), and use of oral contraceptives for 6 years or longer (OR = 0.62; 95% CI = 0.24-1.6). A greater proportion of Black women (48%) than White women (27%) reported four or more term pregnancies, and Black women (62%) were more likely than White women (53%) to have breast-fed their children. Oral contraceptive use was more common among White women (59%) than Black women (51%).** *Conclusion:* **Differences in the prevalence of other factors related to ovarian cancer risk or differences in genetic susceptibility must explain most of the Black-White differences in incidence of ovarian cancer. [J Natl Cancer Inst 85:142–147, 1993]**

The incidence of ovarian cancer is lower among Black women than among White women (*1,2*). In 1988, the age-adjusted incidence rates of ovarian cancer were 10.3 per 100 000 Black women and 15.4 per 100 000 White women (*3*). Fig. 1 shows Black-White differences in age-specific incidence rates for 1984 to 1988. The data are from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER)[1] (*3*).

Epidemiologic studies of ovarian cancer risk have focused chiefly on White women. No study has previously examined risk factors for ovarian cancer among Black women. The purpose of this study was to examine the risk of epithelial ovarian cancer in Black women in relation to reproductive characteristics (e.g., pregnancy, oral contraceptive use, and breast-feeding) and to determine whether these characteristics differ between Black and White women.

Study Population and Methods

Data on ovarian cancer from 12 case-control studies conducted in the United States were combined for collaborative analysis (*4*). Seven (*5-11*) of these studies collected information on epithelial ovarian cancer among Black women. The combined case population included 110 case subjects with a diagnosis of epithelial ovarian cancer between 1971 and 1986. There were 72 invasive cancers, 35 tumors of low malignant potential ("borderline" tumors), and three cancers of unknown tumor behavior. The comparison group comprised 251 population control subjects and 114 hospital control subjects. Control women who had or might have had a bilateral oophorectomy were excluded. Table 1 presents the number of case subjects and control subjects from each study and the sources of the control population.

Interview data from the seven studies were combined, and variables were constructed with common definitions. Details on this procedure are provided elsewhere (*4*). Not all studies collected data on all variables of interest; therefore, the number of case subjects and control subjects available for analysis varied for the different variables.

The collaborative analyses of invasive epithelial ovarian cancers (*12*) and of borderline epithelial tumors (*13*) among White women suggest similar risk factors for these two tumor types. Invasive and borderline tumors, therefore, were combined for the present analysis.

Odds ratios (ORs) and 95% confidence intervals (CIs) for risk of ovarian cancer were estimated by conditional logistic regression (*14*), stratified jointly by study and reference age (16-24, 25-29, . . ., 75-79, 80-88). Reference age refers to age at diagnosis for case subjects and age at interview for control subjects. OR estimates were computed using EGRET software (*15*). All analyses were adjusted for year of birth in order to control for potential bias due to changes over time in reproductive characteristics

*See "Notes" section following "References."

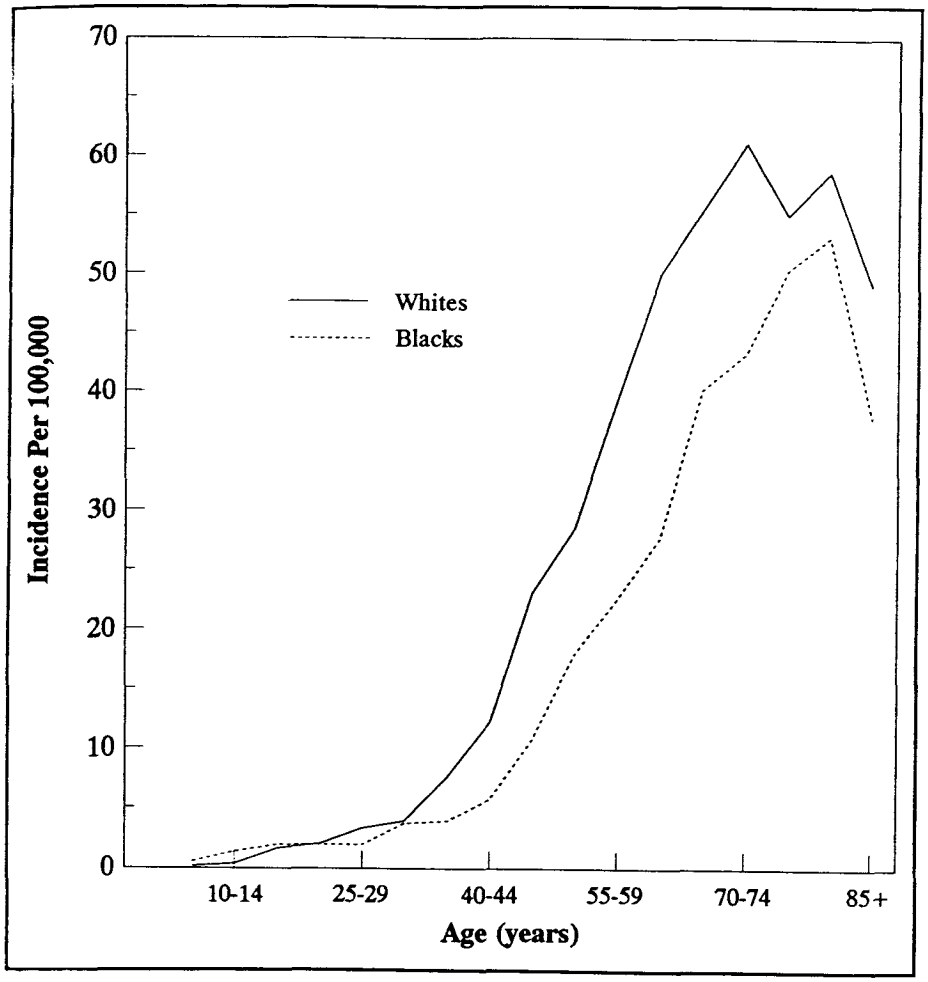

Fig. 1. Age-specific incidence rates for ovarian cancer, SEER data, 1984 to 1988.

such as parity, breast-feeding, or oral contraceptive use.

Black-White differences in incidence could reflect Black-White differences in prevalence of characteristics related to ovarian cancer. To assess this possibility, we compared the prevalence of reproductive characteristics among 246 Black population control subjects [from studies reported in (*6,8,10,11*)] and 4738 White population control subjects [from studies reported in (*6,8,10,11,16*)]. This comparison was restricted to women born after 1919, since White control subjects were born earlier than Black control subjects.

To assess more formally the Black-White differences in epithelial ovarian cancer incidence, we estimated the fraction of Black-White differences in incidence attributable to racial differences in the prevalence of parity, breast-feeding, and oral contraceptive use. To do so, we classified Black and White women into $J = 16$ groups determined by four categories of parity (0, 1, 2-3, and 4+), two categories of breast-feeding (ever, never), and two categories of oral contraceptive use (ever, never). The fraction F of racial differences in incidence attributable to racial differences in prevalence of these characteristics was estimated from the formula

$$F = \frac{1 - (\Sigma_j p_j^b R_j / \Sigma_j p_j^w R_j)}{1 - r}$$

Here, p_j^b and p_j^w represent, respectively, the proportions of Black and White women in group j; R_j represents the ratio of incidence in Whites in group j relative to that in group 1 (an arbitrarily chosen reference group), and r represents the ratio of incidence among Whites to incidence among Blacks in the SEER population. The "Appendix" section contains a derivation of this formula. We estimated the proportions p_j^b and p_j^w from the corresponding proportions among 246 Black and 4738 White control subjects, respectively, and the incidence rate ratios R_j for Whites from the corresponding estimated ORs for White women (*12*). Assuming no dependence on age, these quantities were estimated with control subjects of all ages. However, the ratio r of Black-to-White ovarian cancer incidence rates in the SEER population was calculated separately for women under 50 years of age and those 50 years or older. Thus, the attributable risk fraction F was calculated separately for women in the two age groups.

Results

Women with invasive ovarian cancer were considerably older (mean age, 53.3 years) than women with borderline tumors (mean age, 37.1 years). A greater proportion of case subjects (14%) than control subjects (9%) had never married, but case subjects were similar to control subjects with respect to educational background.

ORs for risk of ovarian cancer associated with reproductive characteristics in Black women are presented in Table 2. Gravidity and parity were negatively related to risk of ovarian cancer. For four or more term pregnancies (>20 weeks' gestation), the OR was 0.53 (95% CI = 0.25-1.1). Term pregnancies were associated with a slightly greater decrease in ovarian cancer risk (12% per pregnancy) than pregnancies of any gestational age (9%

Table 1. Case-control studies of epithelial ovarian cancer including U.S. Black women

Reference	Case subjects*	Year of diagnosis	Control subjects	
			No.*	Source
McGowan et al., 1979 (*5*)	30	1974-1977	27	Case hospitals
Weiss et al., 1981 (*6*)	1	1975-1979	6	Household surveys
Rosenberg et al., 1982 (*7*)	10	1976-1980	37	Case hospitals
Cramer et al., 1983 (*8*)	6	1978-1981	7	Town directories
Hartge et al., 1989 (*9*)	35	1978-1981	46	Case hospitals
CASH† group, 1987 (*10*)	25	1980-1982	235	Random-digit dialing
Whittemore et al., 1988 (*11*)	3	1983-1986	7	Case hospitals (*4*) and random-digit dialing (*3*)

*Number included in present analysis.
†The Cancer and Steroid Hormone Study.

per pregnancy) (Table 2). Among nulliparous women, the OR was 0.58 (95% CI = 0.10-3.2) for those who had ever been pregnant, compared with nulligravid women (Table 2).

Later age at first live birth was associated with a reduced risk of ovarian cancer. The OR was 0.54 (95% CI = 0.19-1.6) for women with their first live birth at age 25 or later, compared with those with their first live birth before age 20.

ORs associated with breast-feeding, oral contraceptive use, and duration of ovulation are presented in Table 3. Among parous women, breast-feeding for 6 months or longer was associated with an OR of 0.85 (95% CI = 0.36-2.0). For oral contraceptive use for 6 or more years, the OR was 0.62 (95% CI = 0.24-1.6). The reduction in risk, however, did not increase with increasing duration of oral contraceptive use. Short-term use for 1 year or less was associated with an OR of 1.8 (95% CI = 0.74-4.4). Adjustment for years of oral contraceptive use did not alter the ORs presented above for gravidity, parity, and breast-feeding.

We estimated the number of years of ovulation by using data on ages at first and last menstruation and duration of pregnancies, breast-feeding, and oral contraceptive use. Longer duration of ovulation was positively associated with the risk of ovarian cancer (Table 3). The OR was 1.6 (95% CI = 0.64-4.0) for women who ovulated for 35 years or longer compared with women with less than 25 years of ovulation.

Few Black women with ovarian cancer reported a history of tubal ligation (n = 13), hysterectomy at least 2 years prior to the reference date (n = 15), or use of menopausal estrogens (n = 4). The corresponding adjusted ORs were 1.1 (95% CI = 0.51-2.5) for tubal ligation, 0.37 (95% CI = 0.18-0.75) for hysterectomy, and 0.49 (95% CI = 0.13-1.8) for menopausal estrogen use. Among women aged 55 years or more with natural menopause, the risk of ovarian cancer increased with increasing age at menopause. Natural menopause at the age of 50 or later was associated with an adjusted OR of 2.8 (95% CI = 0.63-12.5).

Black and White population control subjects differed with respect to selected reproductive factors. A greater proportion of Black women (48%) reported four or more term pregnancies than White women (27%), whereas the proportion of nulliparous women was similar for Blacks (12%) and Whites (13%). A history of breast-feeding was more common for Black women (62%) than for White women (53%). Furthermore, more Black women (42%) than White women (27%) reported breast-feeding for 6 or more months. Oral contraceptive use was more common among Whites (59%) than among Blacks (51%), but the proportion of women who used oral contraceptives for 6 years or longer was similar for Black (22%) and White (21%) women. Differences in the prevalence of these characteristics between Black and White women accounted for only a small proportion of the Black-White differences in incidence of epithelial ovarian cancer. The attributable risk fraction, which was calculated as described in the "Study Population and Methods" section, was 9% among

Table 2. ORs for ovarian cancer among Black women by selected reproductive characteristics

	No. of case subjects*	No. of control subjects	OR†	95% CI
Gravidity				
Nulligravid	21	36	1.0	
Gravid	88	329	0.84	0.43-1.7
1	16	37	0.87	0.35-2.2
2	21	43	1.2	0.52-2.8
3	19	58	0.82	0.35-1.9
≥4	32	191	0.62	0.29-1.3
Trend per pregnancy			0.91	*P* = .14
Parity‡				
Nulliparous	30	55	1.0	
Parous	80	310	0.80	0.44-1.4
1	31	52	1.3	0.65-2.7
2	10	54	0.47	0.19-1.1
3	17	51	0.89	0.40-2.0
≥4	22	153	0.53	0.25-1.1
Trend per term pregnancy			0.88	*P* = .06
Gravidity among nulliparous women				
Nulligravid	21	36	1.0	
Gravid	9	19	0.58	0.10-3.2
Age at first live birth, y§				
<20	27	134	1.0	
20-24	18	92	0.61	0.29-1.3
≥25	9	34	0.54	0.19-1.6
Trend per year			0.95	*P* = .21

*The number of pregnancies was unknown for one case subject.
†ORs adjusted for study, year of birth, and reference age.
‡Term pregnancies (live births and stillbirths) of >20 weeks' gestation.
§Adjusted for parity.

Table 3. ORs for ovarian cancer among Black women by breast-feeding, oral contraceptive use, and duration of ovulation*

	No. of case subjects	No. of control subjects	OR†	95% CI
Breast-feeding among parous women‡				
No	24	102	1.0	
Yes	29	157	0.90	0.42-1.9
1-5 mo	11	52	1.0	0.39-2.6
≥6 mo	18	103	0.85	0.36-2.0
Trend per month of breast-feeding			0.99	P = .57
Use of oral contraceptives‡				
No	77	196	1.0	
Yes	32	168	0.67	0.37-1.2
≤1 y	11	38	1.8	0.74-4.4
2-5 y	9	59	0.34	0.13-.85
≥6 y	10	61	0.62	0.24-1.6
Trend per year of oral contraceptive use			0.92	P = .12
Duration of ovulation, y				
<25	38	135	1.0	
25-34	33	132	1.3	0.59-2.9
≥35	33	65	1.6	0.64-4.0
Trend per year of ovulation			1.04	P = .12

*For breast-feeding, use of oral contraceptives, and years of ovulation, information was unavailable for some subjects.
†ORs adjusted for study, year of birth, and reference age.
‡Adjusted for parity.

women aged less than 50 years and 16% among women aged 50 years and over.

Discussion

The epidemiology of ovarian cancer among Black women has received no attention to date, except for descriptive incidence data. In the present analysis, histories of pregnancy and oral contraceptive use were associated with decreased risk of epithelial ovarian cancer. These findings are consistent with those of previous case-control studies (*17*) comprising primarily White women. Moreover, the findings for Black women are similar to those reported for White women in the collaborative analysis of combined case-control data (*12*).

The combining of data from seven case-control studies has made it possible for the first time to examine reproductive characteristics related to ovarian cancer risk among Black women. Yet the number of Black case subjects was relatively small, and most of the associations did not reach statistical significance, thus limiting inferences. Furthermore, not every study provided data on all variables of interest (e.g., infertility), thus precluding more detailed analysis. Other limitations include potential bias due to nonresponse in the original case-control studies and potential effects of unmeasured characteristics related to ovarian cancer.

Decreased risks of ovarian cancer have been associated consistently with factors that suppress ovulation (e.g., pregnancy, oral contraceptives, or breast-feeding). Ovulation has been proposed to increase ovarian cancer risk through repeated minor trauma to the ovarian surface epithelium (*18,19*). Alternatively, high circulating levels of pituitary gonadotropins may play a pathogenic role in this cancer (*20*). Secretion of pituitary gonadotropins is reduced during pregnancy and oral contraceptive use, which may reduce ovarian cancer risk.

Several studies (*19,21,22*) have reported a positive association between the number of years of ovulation and increased ovarian cancer risk. Among Black women, estimated ovulatory duration of 35 years or longer was associated with a modest increased risk (OR = 1.6), compared with ovulation of less than 25 years. The effect of anovulation or accompanying physiologic events has been reported to vary with the cause for anovulation (i.e., pregnancy, oral contraceptive use, or breast-feeding), thus suggesting that other mechanisms besides anovulation may play a role (*23,24*).

Hysterectomy was associated with reduced ovarian cancer risk, a relationship which is consistent with the findings of the collaborative analysis for White women (*12*). Hysterectomy may impair ovarian function, causing anovulation, or it may prevent exposure to exogenous agents such as talc, which has been associated with increased risk of ovarian cancer (*24*). It is also possible that some women unknowingly had bilateral oophorectomies, although the self-reported number of ovaries removed at hysterectomy has been shown to be accurate (*25*). Another possibility is that women whose ovaries were conserved at hysterectomy because of low subsequent ovarian cancer risk represent a selected population at low ovarian cancer risk (*26*).

In conclusion, risk estimates associated with reproductive factors were similar for Black and White women. While the prevalence of these factors differed between Black and White women, the differences accounted for only a small proportion of the Black-White variation in incidence of epithelial ovarian cancer. Differences in the prevalence of other factors related to ovarian cancer risk or in genetic susceptibility must explain most of the difference in incidence of ovarian cancer.

Appendix

Here, we derive the formula given in the "Study Population and Methods" section for estimating the fraction of Black-White differences in ovarian cancer incidence attributable to Black-White differences in prevalence of risk factors. To derive this formula, we let I^w and I^b represent age-specific ovarian cancer incidence rates among White and Black women, respectively. We have omitted the dependence of the rates on age in order to simplify notation. The fraction F of observed Black-White difference in incidence rates that is attributable to differences in prevalence of the risk factors is

$$F = \frac{I^w - I_*^w}{I^w - I^b}.$$

Here, I_*^w is the incidence rate that would prevail among Whites if their risk factor prevalence equalled that of Blacks. Dividing numerator and denominator by I^w gives

$$F = \frac{1 - I_*^w/I^w}{1 - r}, \qquad [1]$$

where $r = I^b/I^w$ represents the ratio of incidence rates in Blacks to incidence rates in Whites. It remains to derive an explicit expression for the ratio I_*^w/I^w. To do so, we form $J = 16$ groups within each race by classifying women into joint categories of parity (four levels), breast-feeding (two levels), and oral contraceptive use (two levels). Let p_j^w and p_j^b represent the proportions of White and Black women, respectively, in the j^{th} group. The observed incidence rate among Whites is

$$I^w = p_1^w I_1^w + \ldots + p_j^w I_j^w,$$

where I_j^w is the White incidence rate in group j. In contrast, if Whites were distributed among the risk factor groups in the same proportions as Blacks, the White incidence rate would be

$$I_*^w = p_1^b I_1^w + \ldots + p_j^b I_j^w.$$

Thus, we can write

$$\frac{I_*^w}{I^w} = \frac{\Sigma_j p_j^b I_j^w}{\Sigma_j p_j^w I_j^w} = \frac{\Sigma_j p_j^b R_j}{\Sigma_j p_j^w R_j}, \qquad [2]$$

where $R_j = I_j/I_1$ is the ratio of White incidence rates in group j relative to group 1, with $R_1 = 1$. Substituting the right-hand side of equation 2 into equation 1 gives the formula

$$F = \frac{1 - (\Sigma_j p_j^b R_j/\Sigma_j p_j^w R_j)}{1 - r}$$

for the fraction of Black-White differences in incidence attributable to Black-White differences in risk factor prevalence. Notice that this fraction depends on age only through the age dependence of the ethnic-specific prevalences p_j, the White rate ratios R_j, and the Black-to-White rate ratio r.

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Notes

[1]Ed. note: SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

Author affiliations: E. M. John, A. S. Whittemore, R. Harris, J. Itnyre, Division of Epidemiology, Department of Health Research

and Policy, Stanford University School of Medicine.

The Collaborative Ovarian Cancer Group consists of the following individuals: John T. Casagrande, Department of Preventive Medicine, University of Southern California, Los Angeles; Daniel Cramer, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, Mass.; Patricia Hartge, Environmental Epidemiology Branch, National Cancer Institute, Bethesda, Md.; Jennifer L. Kelsey, Division of Epidemiology, Columbia University School of Public Health, New York, N.Y.; Marion Lee, Department of Epidemiology, University of California, San Francisco; Nancy C. Lee, Division of Reproductive Health, Centers for Disease Control and Prevention, Atlanta, Ga.; Joseph L. Lyon, Department of Family and Community Medicine, The University of Utah Medical Center, Salt Lake City; James R. Marshall, Department of Social and Preventive Medicine, State University of New York at Buffalo School of Medicine; Larry McGowan, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, George Washington University Medical Center, Washington, D.C.; Philip C. Nasca, Bureau of Chronic Diseases, Cancer Control Program, New York State Department of Health, Albany; Ralph S. Paffenbarger, Jr., Department of Health Research and Policy, Stanford University School of Medicine, Stanford, Calif.; Lynn Rosenberg, Slone Epidemiology Unit, School of Public Health, Boston University School of Medicine, Boston, Mass.; Noel S. Weiss, Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle; and Genrose D. Copley (Project Consultant), Extramural Programs, Division of Cancer Etiology, National Cancer Institute.

Correspondence to: Esther M. John, Ph.D., Department of Health Research and Policy, Stanford University School of Medicine, HRP Mod. 2, Suite 8, Stanford, CA 94305-5092.

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Increased nm23-H1 and nm23-H2 Messenger RNA Expression and Absence of Mutations in Colon Carcinomas of Low and High Metastatic Potential

Lois L. Myeroff,
*Sanford D. Markowitz**

Background: **The murine nm23 gene suppress malign reduce with i node cancer onstrat nm23 and nm deletio some with p suggest suppre tastasis viously messen is incre tumors static was de vious fi of nm2 colon progno amine activati sis supp nm23-H2 loss of g**

We used ribonuclease protection assays to analyze human colon tumors for the level of nm23-H1 (43 samples) and nm23-H2 (41 samples) transcript (mRNA) expression and the presence of mutations that could inactivate potential suppressor function. *Results:* We detected only wild-type nm23-H1 and nm23-H2 mRNA. Expression of nm23-H1 mRNA increased in 33 of 41 colon tumors, and expression of nm23-H2 mRNA was elevated in 28 of 41 colon tumors relative to that in matched normal mucosa. Increases in these mRNA levels were similar in tumors of both low and high metastatic potential. *Conclusions:* These results suggest that, despite correlation of nm23-H1 allelic deletions with colon cancers associated with poor prognosis, nm23-H1 and nm23-H2 alleles do not directly mediate metastasis suppression in colon carcinoma. Our results leave unexplained the observation that nm23-H1 allelic deletion correlates with metastatic potential of colon carcinomas. *Implications:* These findings also contrast with the dem- nm23 metastasis sup- in murine melanoma correlation of loss of on in breast cancer nosis. It may be that pression by the nm23 -specific phenomenon. Inst 85:147–152, 1993]

metastasis suppressor isolated on the basis of xpression in a non- ie melanoma cell line w-level expression in a ic matched cell line on of nm23 into highly ie melanoma cells re- astatic potential, sug- -23 may be a direct essor (*3*). Two human s of murine nm23 have n23-H1 (*1*) and nm23- genes share a high ogy with the awd de- ie in *Drosophila* (*5*) de diphosphate (NDP) *Dictyostelium* (*6*). The nm23-H2 genes have been shown to be identical to the human NDP kinase A and B chains, respectively (*7*).

The pattern of nm23-H1 gene expression and/or deletion is, in some human tumors, consistent with a metastasis suppressor function. In human breast carcinomas, nm23-H1 messenger

*See "Notes" section following "References."